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10/3

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/485,245	03/27/2000	ALISON HOPKINS	28911/36128	1697

7590 07/12/2004

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EXAMINER

WILDER, CYNTHIA B

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 07/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/485,245	Applicant(s) HOPKINS, ALISON	
	Examiner Cynthia B. Wilder, Ph.D.	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 May 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 7-14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 7-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. <u>4121/04</u> |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

FINAL ACTION

1. Applicant's amendment filed on May 3, 2004 is acknowledged and has been entered. Claims 7-9 have been amended. Claims 1-6 have been canceled. Claims 11-14 have been added. Claims 7-14 are pending and discussed below. All of the amendments and arguments have been thoroughly reviewed and considered but are deemed moot in view of the new grounds of rejections based on Applicant's amendment.

This action is made FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Previous Rejections

3. The claim rejection under 35 USC 112 second paragraph directed to claims 7-10 as being indefinite is withdrawn in view of Applicant's amendment of claim 7. The prior art rejection under 35 USC 103(a) is maintained and discussed below.

Claim Rejections - 35 USC § 103

4. Claims 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godiska et al. (5,759,804, filed November 17, 1993) in view of Shen et al. (EP 0 726 310 A1 February 09, 1996). Regarding claims 7-10, Godiska et al teach a method comprising a random mixture of oligonucleotides which are 6-mers, wherein the composition further contains at least a supply of nucleotides for chain extension, a labeled nucleotide, and a polymerase enzyme (col. 8, lines 27-31). Godiska et al differs from the instant invention in that Godiska et al do not expressly teach wherein the solution comprising the random mixture of hexamers is in a freeze-dried state. Shen

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et al teach a method and composition similar to that of Godiska et al, wherein the reagents of the composition are in a dry state (page 4, lines 37-41). Shen et al teach wherein the composition may comprise primers, a polymerase enzyme, a supply of nucleotides for chain extension, and a stabilizer, wherein said reagents of the composition are in a freeze-dried state (page 6, lines 3-7 and 22). Shen et al teach that a composition present in the dry state is advantageous because the composition is stable for a prolonged period, even when stored at high temperature. Shen et al further teach that a composition in a dried state is useful in shipping and storage of commercial preparations for use in e.g., nucleic acid amplification kits (page 6, lines 39-41). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have been motivated to have provided a random mixture of hexamers in the method as taught by Godiska et al in a dried state. One of ordinary skill in the art would have been motivated to do so for the advantage taught by Shen et al that a nucleic acid composition (such as primers) present in a dried state is useful in shipping and storage of commercial preparations due its increase stability.

Applicant's Traversal

5. Applicant traverses the rejection on the following grounds: Applicant states Applicant's invention is not anticipated by any of the prior art. Applicant states that as discussed in the interview, the application examples demonstrate a critical and unexpected difference in self-priming activity and labeling intensity between 6-8 mers and 9-mers and there is no suggesting in the art that such a difference could occur. Applicant states that accordingly, the obviousness rejection under 35 USC 103(a) should be withdrawn because the art fails to teach the desirability of short primers in a dried primer system or that 6-mers to 8-mersf would behave differently with

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respect to self-priming activity and labeling intensity than do 9-mers. Applicant states that more specifically, Godiska discloses liquid 6-mers but fails to teach (1) that the selection of 6-mers to 8-mers constitutes a critical range or (2) that short primers (6-8 mers) would be desirable in a dried primer system. Applicant states that while Godiska discloses a random mixture of 6-mers and other ingredients the Examiner acknowledges that Godiska does not teach a labeling composition in a dry state. Applicant states that more over, there is nothing in Godiska that teaches that the selections of 6-mers to 8-mers is important in either the liquid or freeze dried state to reduce self-annealing. Applicant states that in fact, self-annealing is not mentioned at all. Applicant further asserts that Shen discloses dried 48-mers and 22-mers primers but fail to suggest that such dried primers should be shortened (or alternatively any reason why the short primers of Godiska should be dried). This is because the prior art generally taught that longer primers were preferred because longer primers have higher melting temperatures and are thus more specific. Applicant contends that moreover, Shen acknowledges that "whether a particular composition will function to preserve biological activity for a particular biologically active material is not *a priori* predictable" and only discloses freeze-drying as an "option. Applicant states that in addition, Shen fails to provide any reason why the primers of Godiska should be dried, given the fact that shorter primers were thought to be inherently more stable and that there was no reasons to believe that the shorter Godiska primers would benefit from being in a freeze-dried kit. Applicant concludes that the rejections should be withdrawn

Examiner's Response

6. All of the arguments and amendments filed on May 3, 2004 have been thoroughly reviewed and considered but they are not found persuasive for the reasons that follow: In

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response to Applicant's arguments that the rejection should be withdrawn because the art fails to teach the desirability of short primers in a dried primer system or that 6-mers to 8-mers would behave differently with respect to self-priming activity and labeling intensity than do 9-mers, it is noted that the features upon which applicant rely are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Likewise, the courts have established that during patent examination, the claims must be interpreted broadly as reasonably allow (*In re Zletz*, 893 F.2d 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989)). In this case, the claims as broadly written are *not limited* in the way Applicant contends nor do the claims recite any features which would suggest the desirability of short primers in a dried primer system or that 6-mers to 8-mers would behave differently with respect to self-priming activity and labeling intensity than do 9-mers. There is nothing in the claims that indicates that random primers 6-mers to 8-mers in a dried state results in forming a random mixture of oligonucleotides which are resistant to self-annealing. More specifically, there are no limitations in the claims that would suggest that such results were achieved. Thus the claims do not describe the steps or characteristics, which distinguishes them from the prior art.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the primary reference, Godiska et al., is cited for its teaching of a method comprising a random mixture of 6-mers oligonucleotide as required by the claims 6 and 10 and reagents for a chain extension assay

as required by claim 9. As stated in the prior Office action of 1/29/2004, Godiska et al do not expressly teach wherein the 6-mers are in a dried state. However, this limitation is provided in the teachings of the secondary reference by Shen. As noted above, Shen et al teach a method and composition comprising primers in a dried state and reagents for chain extension as required by claims 7 and 8. Shen provides motivation for providing the primer and other reagents required for chain extension in a dry state. To reiterate, Shen et al teach that a composition present in the dry state is advantageous because the composition is stable for a prolonged period, even when stored at high temperature. Shen et al further teach that a composition in a dried state is useful in shipping and storage of commercial preparations for use in e.g., nucleic acid amplification kits. Thus, the combined teaching of Godiska et al in view of Shen et al establishes a case of obviousness over the instant over the instant invention. MPEP 8th edition states that "[T]he test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference....Rather, the test is what the combined teaching of those references would have suggested to those of ordinary skill in the art " *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). See also *In re Sneed*, 710 F.2d 1544, 1550, 218 USPQ 385, 389 (Fed. Cir. 1983) ("[I]t is not necessary that the inventions of the references be physically combinable to render obvious the invention under review."); and *In re Nievelt*, 482 F.2d 965, 179 USPQ 224, 226 (CCPA 1973) ("Combining the teachings of references does not involve an ability to combine their specific structures").

Applicant is once again advised that unexpected results as indicted by Applicant must correlate with the invention provided in the specification. While the claims broadly recite a method of forming a random mixture of oligonucleotides which is resistant to self-annealing as

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recited in the claims 7-10, the specification on the other hand illustrates a reduction in the percentage of self-priming when utilizing oligonucleotides 6-mers to 8-mers versus 9-mers but does not illustrate a resistance to self-annealing by selecting a mixture of said oligonucleotides. The specification further teaches that the percentage or rate of dCTP incorporation is critical to the self-priming abilities of the random primers that are 6-mers to 8-mers versus primers that are nanomers. The claims must make clear the discovery of the unexpected results as supported by the specification as originally filed.

In view of the foregoing, Applicant's arguments are not sufficient to overcome the prior art rejections. Accordingly, the rejection under 35 U.S.C. 103(a) is maintained.

New Ground(s) of Rejections

**THE NEW GROUND(S) OF REJECTIONS WERE NECESSITATED BY
APPLICANT'S AMENDMENT TO THE CLAIMS:**

Claim Rejections - 35 USC § 112 first paragraph: New Matter

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method of forming a random mixture of oligonucleotides

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which is resistant to self-annealing comprising the steps of selecting a random mixture of oligonucleotides which are 6-mers to 8-mer and drying said mixture. Applicant provides no cited support for the new limitation "oligonucleotides which is resistant" and thus a review of the specification as originally filed does not support or depict what is claimed. While the specification illustrates as a group a reduction in the percent (%) of self-priming when utilizing mixtures of oligonucleotides which are 6-mer to 8mers versus oligonucleotides which are 9-mers, there is no disclosure which illustrates whether or not the reduction in % of self-priming is due to a "selection process" of oligonucleotides having a self annealing resistant property or whether or not the reduction in % self-priming is due to an interaction between the random oligonucleotides or whether or not the reduction in the % of self priming is due the sequences of the oligonucleotides. No support has been found anywhere in the specification which suggests that the oligonucleotides of the invention are "resistant" to self-priming or "resistant" to self-annealing. Therefore, the specification would not have suggested to the skilled artisan that the Applicant was in possession of the claimed invention as of filing date.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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10. Claims 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godiska et al. (5,759,804, filed November 17, 1993) in view of Shen et al. (EP 0 726 310 A1 February 09, 1996). Regarding claims 11-14, Godiska et al teach a method comprising a random mixture of oligonucleotides which are 6-mers, wherein the composition further contains at least a supply of nucleotides for chain extension, a labeled nucleotide, and a polymerase enzyme (col. 8, lines 27-31). Godiska et al differs from the instant invention in that Godiska et al do not expressly teach wherein the solution comprising the random mixture of 6-mers is in a freeze-dried state. Shen et al teach a method and composition similar to that of Godiska et al, wherein said composition is present in a dry state (page 4, lines 37-41). Shen et al teach wherein the composition may comprise primers, a polymerase enzyme, a supply of nucleotides for chain extension, and a stabilizer (page 6, lines 3-7 and 22). Shen et al teach that the composition present in the dry state is advantageous because the composition is stable for a prolonged period, even when stored at high temperature. Shen et al further teach that a composition in a dried state is useful in shipping and storage of commercial preparations for use in e.g., nucleic acid amplification kits (page 6, lines 39-41). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have been motivated to have provided the random mixture of 6-mers in the method as taught by Godiska et al in a dried state for the advantage taught by Shen et al that a nucleic acid composition (such as primers) present in a dried state is useful in shipping and storage of commercial preparations due its increase stability, even when stored for prolonged periods or when stored at high temperatures.

Claim Rejections - 35 USC § 112 second paragraph: Indefiniteness

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 7-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 7-10 are indefinite at the step of "selecting" a random mixture of oligonucleotides because the specification and claims does not define what is meant by "selecting" and it is unclear how one is to distinguish or "select" an oligonucleotide which is 6-mer to 8-mer from another oligonucleotide 6-mer to 8-mer to obtain its self-annealing resistance properties. Clarification is required.

(b) Claims 7-10 is because the claims lack a final process step in claim 7 that clearly relates back to the preamble. The claims are drawn to "a method of forming a random mixture of oligonucleotides which is resistant to self-annealing". However, the final step recites a step of "drying said mixture". Thus it cannot be determined if the goal of the preamble, i.e., forming a random mixture of oligonucleotides which is resistant to self-annealing is achieved or not, and if achieved, in what step. Likewise, it cannot clearly be determined if the claims are intended to recited "a method of drying a mixture of random oligonucleotide which are 6-mers to 8-mers" or "a method of forming a random mixture of oligonucleotides which is resistant to self-annealing". While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion (see *ex parte Erlich*, 3 UsPQ2d1011, p.1011 (Bd. Pat. Applicant. Int.1986). Clarification is required as to Applicant's intent.

Conclusion

13. No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

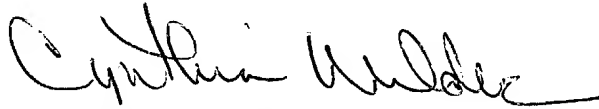
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



CYNTHIA WILDER
PATENT EXAMINER

7/7/2009